

## REMARKS

Applicants affirm the provisional election made on 18 April 2001.

The specification has been amended to correct the typographical errors noted by the Examiner. Claims 1-19 have been canceled without prejudice to filing in a continuation application. Claims 37-47 have been canceled without prejudice to filing a divisional application. Claim 32 has been canceled. Claim 20 has been amended to delete the peptide J010. Claims 27-31 and 33-36 have been amended to set forth the SEQ ID NO: as found in Claim 20. It is believed that none of these amendments constitute new matter and their entry is requested.

Applicants note the Examiner's objection to claims 27-36 with respect to complying with the sequence rules. The claims have been amended to set forth the appropriate SEQ ID NO: as found in claim 20. Since the sequences have already been included in both the paper copy and the computer readable form of the Sequence Listing which was filed on 6 December 1999, it is submitted that no further paper copy or computer readable form of the Sequence Listing is necessary.

Applicants note the Examiner's objection to the Watkins Declaration. A fresh Declaration and Power of Attorney executed by inventor Watkins is attached hereto.

The Examiner rejected claims 1-4, 6-10, 13-14, 16-20, 21, 23 and 25 under 35 USC §112, first paragraph for, in essence, new matter. Applicants note that the Examiner specifically made this rejection with respect to claims 1 and 7. Thus, the rejection is not proper to claims 20-36 which do not depend from either claims 1 or 7 and do not contain the objected language. Applicants further note that the specification as filed fully supports the proviso found in claims 1 and 7, since the original specification stated that the C-terminus (i.e., Xaa<sub>7</sub>) was des-Xaa, or a peptide of 2-9 amino acids. However, in an effort to expedite prosecution of this application, claims 1-19 have been canceled. The cancellation of claims 1-19 is believed to obviate the rejection and its withdrawal is requested.

The Examiner rejected claims 1-4, 6-10 and 13 under 35 USC §112, first paragraph for lack of written description. It is submitted that Applicants were in possession of the generic formulas set forth in the specification, since these formulas specified each of the potential amino acids at each of the variable residues, and set forth the common features of the members of the group. Clearly a

B

skilled artisan could recognize from these generic formulas that Applicant was in possession of the specified generic formulas. However, in an effort to expedite prosecution of this application, claims 1-19 have been canceled. The cancellation of claims 1-19 is believed to obviate the rejection and its withdrawal is requested.

The Examiner rejected claims 1-4, 6-10, 13-14, 16-20, 21, 23, 25, 28 and 32 under 35 USC §112, first paragraph for lack of enablement. It is believed that this rejection, at best, is only proper with respect to claims 1-19 and not with respect to claims 20-31 and 33-36. In fact, the reasons provided by the Examiner concerning lack of enablement are directed to the broad claims (i.e., claims 1-19) and not the specific claims (i.e., claims 20-31 and 33-36). Furthermore, the reasons provided by the Examiner with respect to variable substituents clearly cannot apply to claims 27-31 and 33-36, which do not contain substituents. Although Applicants believe that the specification is fully enabling with respect to the complete scope of the disclosed invention, Applicants have canceled claims 1-19 in order to expedite the prosecution of application.

Claims 27-31 and 33-36 are directed to specific  $\gamma$ -conopeptides, having no variable amino acid residues. Claims 20-26 are directed to specific  $\gamma$ -conopeptides having variable amino acid residues (i.e., Xaa<sub>1</sub>, Xaa<sub>2</sub> or Xaa<sub>3</sub>) in which the residue variable amino acid residue is one of two substituents well known to have activity in conopeptides. For example, Xaa<sub>3</sub> may be Pro or Hyp, amino acids well known to be present in conopeptides and well known to skilled artisans to impart biological activity in conopeptides. The Examiner's attention is directed to the cited Olivera patent (US 5,432,155), for example, which discloses conopeptides having Pro or Hyp. Similarly, Fainzilber et al. (Biochem 34:8649-56 (1995); a copy provided with the IDS filed 6 December 1999) discloses a conopeptide having Pro or Hyp and Glu or  $\gamma$ -carboxy-Glu (Gla) residues. In addition, conopeptides containing Trp or bromo-Trp are described in Cruz et al. (US 5,889,147). Thus, each of the specified substituents for the specific  $\gamma$ -conopeptides set forth in claims 20-27) are well known in conopeptides, and conopeptides containing such substituents are well known to have biological activity. Thus, skilled artisans know that the specified substituents have biological activity within the conopeptide framework, and a skilled artisan would predict with reasonable certainty that these same substituents would have biological activity within the claimed  $\gamma$ -conopeptides.

B

conopeptides. Consequently, it is submitted that there is sufficient guidance in the specification to enable the  $\gamma$ -conopeptides of claims 20-31 and 33-36.

Furthermore, Applicants are unable to find any disclosure at page 99, second column of Shen et al. cited by the Examiner to suggest that claims 20-31 and 33-36 are not enabled by the specification. In addition, it is submitted that Shen et al. does not demonstrate that species variation in the hypervariable loop region results in distinct pharmacological activities. For example, all  $\alpha$ -conopeptides of the 3/5 type are specific for nicotinic acetylcholine receptors at the neuromuscular junction, regardless of the specific amino acid residues within the 3/5 loops. Thus, variations of the amino acid sequence within the loop structure was known to a skilled artisan not to change the basic biological activity of the conopeptide. Consequently, a skilled artisan would be able to predict with reasonable certainty that the changes in amino acid residues within the loops of the claimed  $\gamma$ -conopeptides would not change the receptor target. Thus, it is submitted that the specification is fully enabling for claims 20-31 and 33-36.

In view of the cancellation of claims 1-19 and the reasons discussed above, it is believed that the specification fully enables the presently claimed invention as set forth in claims 20-31 and 33-36. Withdrawal of this enablement rejection is requested.

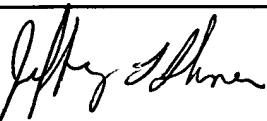
The Examiner rejected claims 1-4, 6-10, 13-14, 16-20, 21, 23, 25, 28 and 32 under 35 USC §112, second paragraph for being indefinite. It is believed that the cancellation of claims 1-19 and 32 and the amendment of claims 20-31 and 33-36 to include the SEQ ID NO: for the designated peptides obviate this rejection. Withdrawal of this rejection is requested.

The Examiner rejected claims 1-3, 6-9, 13, 20, 21 and 32 under 35 USC §102(b) as being anticipated by Olivera et al. (US 5,432,155) for its disclosure of J010. It is believed that the cancellation of claims 1-19 and 32 and the deletion of this peptide from claim 20 obviates this rejection. Withdrawal of this rejection is requested.

The Examiner rejected claims 1, 7 and 13 under 35 USC §102(b) as being anticipated by Eldridge et al. (*J. Virology* 66:6563-6571). It is believed that the cancellation of claims 1-19 obviates this rejection, and its withdrawal is requested.

B

In view of the above amendments and remarks, it is believed that the present claims satisfy the provisions of the patent statutes and are patentable over the cited prior art. Reconsideration of the application and early notice of allowance are requested. The Examiner is invited to telephone the undersigned to expedite the prosecution of the application.

RESPECTFULLY SUBMITTED,					
NAME AND REG. NUMBER	Jeffrey L. Ihnen, Registration No. 28,957				
SIGNATURE				DATE	24 October 2001
ADDRESS	Rothwell, Figg, Ernst & Manbeck, P.C. 555 Thirteenth Street, N.W., Suite 701, East Tower				
CITY	Washington	STATE	D.C.	ZIP CODE	20004
COUNTRY	U.S.A.	TELEPHONE	(202) 783-6040	FAX	(202) 783-6031

Attachments: Marked-Up Copies of Amendments  
Declaration and Power of Attorney of Maren Watkins

b

**Marked-up Copy of Amended Paragraph at Page 2, lines 10-21:**

Several peptides isolated from *Conus* venoms have been characterized. These include the  $\alpha$ -,  $\mu$ - and  $\omega$ -conotoxins which target nicotinic acetylcholine receptors, muscle sodium channels, and neuronal calcium channels, respectively (Olivera et al., 1985). A conotoxin, TxVIIA, containing a  $\gamma$ -carboxyglutamate [residued] residue and three disulfide bonds has [bee] been isolated (Fainzilber et al., 1991). Conopressins, which are vasopressin analogs, have also been identified (Cruz et al.. 1987). In addition, peptides named conantokins have been isolated from *Conus geographus* and *Conus tulipa* (Mena et al., 1990; Haack et al., 1990). These peptides have unusual age-dependent physiological effects: they induce a sleep-like state in mice younger than two weeks and hyperactive behavior in mice older than 3 weeks (Haack et al., 1990). Recently, peptides named contryporphans containing D-tryptophan or D-leucine residues have been isolated from *Conus radiatus* (U.S. Serial No. 09/061,026), and bromo-tryptophan conopeptides have been isolated from *Conus imperialis* and *Conus radiatus* (U.S. Serial No. 08/785,534).

**Marked-up Copy of Amended Paragraph at Page 2, line 22 - page 3, line 2:**

Ion channels are integral plasma [membran] membrane proteins responsible for electrical activity in excitable tissues. It has been recognized that slow inward currents can influence neuronal excitability via long-lasting depolarizations of the cell membrane (Llinás, 1988). The role of slow inward currents in generating endogenous bursting behavior has been recognized in molluscan neurons (Wilson & Wachtel, 1974; Eckert & Lux, 1976; Partridge et al., 1979), and more recently in some types of mammalian neurons (Lanthorn et al., 1984; Stafstrom et al., 1985; Llinás, 1988; Alonso & Llinás, 1989). Changes in the slow inward currents carried by such nonspecific cation channels may play a crucial role in bursting and pacemaker activities in a variety of excitable systems, ranging from mammalian heart muscle to molluscan neurons (Partridge & Swandulla, 1988; Hoehn et al., 1993; Kits & Mansvelder, 1966; van Soest & Kits, 1997). Slow inward currents are also believed to be important in generating epileptiform bursting in regions of the brain such as the hippocampus.

### **Marked-up Copy of Amended Claims**

20 (amended). A substantially pure conopeptide selected from the group consisting of:

(a) PnVIIA: Asp-Cys-Thr-Ser-Xaa<sub>1</sub>-Phe-Gly-Arg-Cys-Thr-Val-Asn-Ser-Xaa<sub>2</sub>-Cys-Cys-Ser-Asn-Ser-Cys-Asp-Gln-Thr-Tyr-Cys-Xaa<sub>2</sub>-Leu-Tyr-Ala-Phe-Xaa<sub>3</sub>-Ser (SEQ ID NO:6);

(b) Tx6.4: Xaa<sub>1</sub>-Leu-Xaa<sub>2</sub>-Cys-Ser-Val-Xaa<sub>1</sub>-Phe-Ser-His-Cys-Thr-Lys-Asp-Ser-Xaa<sub>2</sub>-Cys-Cys-Ser-Asn-Ser-Cys-Asp-Gln-Thr-Tyr-Cys-Thr-Leu-Met-Xaa<sub>3</sub>-Xaa<sub>3</sub>-Asp-Xaa<sub>1</sub> (SEQ ID NO:7);

(c) Tx6.9: Xaa<sub>1</sub>-Xaa<sub>1</sub>-Arg-Xaa<sub>1</sub>-Gly-Gly-Cys-Met-Ala-Xaa<sub>1</sub>-Phe-Gly-Leu-Cys-Ser-Arg-Asp-Ser-Xaa<sub>2</sub>-Cys-Cys-Ser-Asn-Ser-Cys-Asp-Val-Thr-Arg-Cys-Xaa<sub>2</sub>-Leu-Met-Xaa<sub>3</sub>-Phe-Xaa<sub>3</sub>-Xaa<sub>3</sub>-Asp-Xaa<sub>1</sub> (SEQ ID NO:8);

[(d) J010: Cys-Lys-Thr-Try-Ser-Lys-Try-Cys-Xaa<sub>2</sub>-Ala-Asp-Ser-Xaa<sub>2</sub>-Cys-Cys-Thr-Xaa<sub>2</sub>-Gln-Cys-Val-Arg-Ser-Tyr-Cys-Thr-Leu-Phe (SEQ ID NO:9);]

([e] d) Tx6.6: Asp-Xaa<sub>1</sub>-Xaa<sub>1</sub>-Asp-Asp-Gly-Cys-Ser-Val-Xaa<sub>1</sub>-Gly-Xaa<sub>3</sub>-Cys-Thr-Val-Asn-Ala-Xaa<sub>2</sub>-Cys-Cys-Ser-Gly-Asp-Cys-His-Xaa<sub>2</sub>-Thr-Cys-Ile-Phe-Gly-Xaa<sub>1</sub>-Xaa<sub>2</sub>-Val (SEQ ID NO:10);

([f] e) Tx6.5: Gly-Met-Xaa<sub>1</sub>-Gly-Xaa<sub>2</sub>-Cys-Lys-Asp-Gly-Leu-Thr-Thr-Cys-Leu-Ala-Xaa<sub>3</sub>-Ser-Xaa<sub>2</sub>-Cys-Cys-Ser-Xaa<sub>2</sub>-Asp-Cys-Xaa<sub>2</sub>-Gly-Ser-Cys-Thr-Met-Xaa<sub>1</sub> (SEQ ID NO:11);

([g] f) Gm6.7: Xaa<sub>2</sub>-Cys-Arg-Ala-Xaa<sub>1</sub>-Tyr-Ala-Xaa<sub>3</sub>-Cys-Ser-Xaa<sub>3</sub>-Gly-Ala-Gln-Cys-Cys-Ser-Leu-Leu-Met-Cys-Ser-Lys-Ala-Thr-Ser-Arg-Cys-Ile-Leu-Ala-Leu (SEQ ID NO:12);

([h] g) Mr6.1: Asn-Gly-Gln-Cys-Xaa<sub>2</sub>-Asp-Val-Xaa<sub>1</sub>-Met-Xaa<sub>3</sub>-Cys-Thr-Ser-Asn-Xaa<sub>1</sub>-Xaa<sub>2</sub>-Cys-Cys-Ser-Leu-Asp-Cys-Xaa<sub>2</sub>-Met-Tyr-Cys-Thr-Gln-Ile (SEQ ID NO:13);

([i] h) Mr6.2: Cys-Gly-Gly-Xaa<sub>1</sub>-Ser-Thr-Tyr-Cys-Xaa<sub>2</sub>-Val-Asp-Xaa<sub>2</sub>-Xaa<sub>2</sub>-Cys-Cys-Ser-Xaa<sub>2</sub>-Ser-Cys-Val-Arg-Ser-Tyr-Cys-Thr-Leu-Phe (SEQ ID NO:14); and

([j] i)Mr6.3: Asn-Gly-Gly-Cys-Lys-Ala-Thr-Xaa<sub>1</sub>-Met-Ser-Cys-Ser-Ser-Gly-Xaa<sub>1</sub>-Xaa<sub>2</sub>-Cys-Cys-Ser-Met-Ser-Cys-Asp-Met-Try-Cys (SEQ ID NO:15),  
wherein Xaa<sub>1</sub> is Trp or 6-bromo-Trp; Xaa<sub>2</sub> is Glu or  $\gamma$ -carboxyglutamic acid ( $\gamma$ -Glu); and Xaa<sub>3</sub> is Pro or hydroxy-Pro (Hyp).

27 (amended). The conopeptide of claim 20, wherein the conopeptide is PnVIIA (SEQ ID NO:6) and wherein Xaa<sub>1</sub> is Trp, Xaa<sub>2</sub> is  $\gamma$ -Glu, Xaa<sub>3</sub> is Hyp and the C-terminus has a free carboxyl group.

28 (amended). The conopeptide of claim 20, wherein the conopeptide is Tx6.4 (SEQ ID NO:7) and wherein Xaa<sub>1</sub> is Trp, Xaa<sub>2</sub> is  $\gamma$ -Glu, Xaa<sub>3</sub> is Hyp and the C-terminus has a free carboxyl group.

29 (amended). The conopeptide of claim 20, wherein the conopeptide is Tx6.9 (SEQ ID NO:8) and wherein Xaa<sub>1</sub> is Trp, Xaa<sub>2</sub> is  $\gamma$ -Glu, Xaa<sub>3</sub> is Hyp and the C-terminus has a free carboxyl group.

30 (amended). The conopeptide of claim 20, wherein the conopeptide is Tx6.6 (SEQ ID NO:10) and wherein Xaa<sub>1</sub> is Trp, Xaa<sub>2</sub> is  $\gamma$ -Glu, Xaa<sub>3</sub> is Hyp and the C-terminus has a free carboxyl group.

31 (amended). The conopeptide of claim 20, wherein the conopeptide is Tx6.5 (SEQ ID NO:11) and wherein Xaa<sub>1</sub> is Trp, Xaa<sub>2</sub> is  $\gamma$ -Glu, Xaa<sub>3</sub> is Hyp and the C-terminus has a free carboxyl group.

33 (amended). The conopeptide of claim 20, wherein the conopeptide is Gm6.7 (SEQ ID NO:12) and wherein Xaa<sub>1</sub> is Trp, Xaa<sub>2</sub> is  $\gamma$ -Glu, Xaa<sub>3</sub> is Hyp and the C-terminus has a free carboxyl group.

B

34 (amended). The conopeptide of claim 20, wherein the conopeptide is Mr6.1 (SEQ ID NO:13) and wherein Xaa<sub>1</sub> is Trp, Xaa<sub>2</sub> is  $\gamma$ -Glu, Xaa<sub>3</sub> is Hyp and the C-terminus is amidated.

35 (amended). The conopeptide of claim 20, wherein the conopeptide is Mr6.2 (SEQ ID NO:14) and wherein Xaa<sub>1</sub> is Trp, Xaa<sub>2</sub> is  $\gamma$ -Glu and the C-terminus is amidated.

36 (amended). The conopeptide of claim 20, wherein the conopeptide is Mr6.3 (SEQ ID NO:15) and wherein Xaa<sub>1</sub> is Trp, Xaa<sub>2</sub> is  $\gamma$ -Glu and the C-terminus is amidated.